# Implementation of lung cancer screening in Europe: challenges and potential solutions - Summary of a multidisciplinary roundtable discussion

**Key words**: Lung cancer screening, patient recruitment, nodule management, lung cancer mortality, secondary care pathways, multi-disciplinary clinics, implementation planning.

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**Abstract**

Recent randomised trials on screening with low-dose computerised tomography (CT) have shown important reductions in lung cancer (LC) mortality and have triggered international efforts to implement LC screening. Detection rates of stage I LC with volume CT approaching 70% have been demonstrated.

In April 2019 "ESMO Open – Cancer Horizons" convened a roundtable discussion on the challenges and potential solutions regarding the implementation of LC screening in Europe. The expert panel reviewed the current evidence for LC screening with low dose CT and discussed next steps which are covered in this article. The panel concluded that national health policy groups in Europe should start to implement CT screening as adequate evidence is available. It was recognised that there are opportunities to improve the screening process through 'Implementation Research Programmes'.

**Introduction**

Recent large randomised trials on low-dose computerised tomography (CT) screening including the American National Cancer Institute (NCI)-sponsored National Lung Screening Trial (NLST) as well as the Dutch/Belgian NELSON (Nederlands-Leuvens Longkanker Screenings Onderzoek) trial have shown significant reductions in LC mortality of 20-26% and have triggered international efforts to implement LC screening (1-3) . As demonstrated by results from the International Early LC Action Project (I-ELCAP) and the NELSON clinical trials groups, detection rates of stage I LC with volume CT could approach 70%.

In April 2019 "ESMO Open – Cancer Horizons" convened a roundtable discussion on the challenges and potential solutions regarding the implementation of LC screening in Europe. The expert panel reviewed the current evidence for LC screening with low dose CT and discussed next steps which are covered in this article.

Figure 1 shows levels of evidence for implementation of LC screening in Europe.

**Figure 1: Levels of evidence for implementation of LC screening in Europe (4)**

Amended/updated in 2019 from a figure published in (4) in 2016.
Colour codes: green: sufficient evidence; amber: borderline evidence
Abbreviations: CT, computerised tomography; UKLS, United Kingdom Lung Cancer Screening Trial; NELSON, Nederlands-Leuvens Longkanker Screenings Onderzoek ;NLST, National Lung Screening Trial ; QALY, quality-adjusted life year; MDT, multi-disciplinary team; NICE, national institute for health and care excellence; LDCT, low dose CT; VDT, volume doubling time; LLP, Liverpool Lung Project; PLCO, Prostate, Lung, Colorectal and Ovarian Cancer Screening Trial.

**Recruitment for national LC screening programmes**

The aim regarding recruitment for national LC screening programmes is to achieve an informed participation focusing on high-risk (hard-to-reach) individuals. Those at highest risk of lung cancer are those who are most likely to benefit from screening (even when considering co-morbidity); however, they are less likely to participate in LC screening and are more likely to be of lower socioeconomic background and to be current smokers (4) .

**Recruitment challenges**

*Screening approaches*
It is a difficult balance between the availability of systematic risk data of a relatively large group of approachable individuals (health registers, primary care registers, questionnaires, online surveys) and ensuring equity: versus the less systematic and less costly approaches for smaller groups, which are likely to be the worried-well (through clinics and advertising).

*Age*
It has been argued whether to start recruitment at age 60 or 55. Screening strategies for Switzerland indicate a starting age of 60, and include those up to 79 years of age. The National

Health Service (NHS) England Protocol (5) however argues for screening between 55 to 75 years of age. A number of risk prediction models have been developed, of which the Prostate, Lung, Colorectal and Ovarian Cancer Screening Trial $(PLCO)_{2012}$ (6) (1.6% risk over 6 years) and the Liverpool Lung Project $(LLP)_{v2}$ (7, 8) ( 2.5% risk over 5 years) have both been included in the recent NHS England Protocol.
In the United States of America (USA), the United States Preventive Services Task Force (USPSTF) (9) on LC screening has a much less stringent selection criteria, which is based on the NLST trial and the Cancer Intervention and Surveillance Modelling Network (CISNET) modelling (10).

*Smoking*
Some consider one basic inclusion question would suffice "have you ever smoked?" .

*Information technology*
Investment into information technology systems are needed to collate patients' risk data and also to manage and monitor LC CT screened patients. In the UK this has recently been amplified by Sir Professor Richard's Interim Report on UK Cancer screening (11).

**Role-out of LC in Europe**

The roundtable panel recognised that LC screening can be initiated in Europe, however there is room for improvement in several areas and the recommendation discussed, is provided in Figure 2.

**Figure 2: European implementation trials needed**

Source: private communication de Koning and van der Aalst

**LC screening**

***(i) Radiology protocol***

The most recent European protocol of the management of CT detected nodules was published in the Lancet Oncology 2017 (3) which was developed as a consensus document by experts from nine countries within Europe. Using volume doubling time (VDT) biomarker reduces invasive procedures, biopsies and surgery by tenfold (12) compared to the NLST data (1).

Recently, it has been recognised that new nodules are common in follow-up CT scans (3-13% screenings) (13) (14) and comprise a significantly higher LC probability, which are at smaller size, thus the recommendation for new nodules during the screening process

This more stringent cut-off values should be mandatory:

• Negative screen result: <30mm3 (LC probability <1%)

• Indeterminate screen result: 30-200mm3 (LC prob ~3%)

• Positive screen result: >200mm3 (LC prob ~17%).

### *(i) Screening interval*

The screening interval, annual versus biennial, has been debated in the literature (15-17), however, clearly the optimal screen intervals should consider using the previous CT screen results to estimate LC risk. However, in the light of the recent NELSON results given at the World Conference on Lung Cancer (WCLC) 2018 (2), the annual screening frequency is considered the default until more data supporting other approaches may be available. However, it is recognised that there is a potential avenue to select individuals with a low risk of developing lung cancer utilising their base line scan and depending on their overall risk profile, could be considered for biennale screening (18-20), this would need continues monitoring during the screening lifetime of the patient.

### *(ii) Quality assurance*

Quality assurance (QA) in CT screening has been poorly implemented. Therefore, the prospect of setting up LC CT Screening Imaging Core laboratories for QA as well as benchmarking the automated CT scan software and post-processing procedures are attractive options. However mature, validated tools for these purposes are not yet widely available. In the meantime, there is a preference for the delivery of LC screening care in dedicated clinical centres of excellence and using virtual central reading of the CT scans.

### *(iii) Mortality reduction in women*

The NELSON presentation at WCLC 2018 provides evidence for lung cancer mortality reduction in women (39-61%) (2, 21). In the NLST this figure was 27% for women (Figure 3). The implication for the higher mortality gain in women compared to men is poorly understood and requires further investigation.

**Figure 3: LC CT screening: NLST and NELSON Mortality data presented at the WCLC 2018**

Source: data provided by de Koning H. at WCLC 2018 (2, 21)

### *(iv) Prolonged low dose CT screening*

The Multicentric Italian Lung Detection (MILD) trial recently evaluated the benefit of prolonged low dose CT screening beyond 5 years, and its impact on overall and LC specific mortality at 10 years (22). MILD prospectively randomised 4099 participants, to a screening arm (n ¼ 2376), with further randomization to annual (n ¼ 1190) or biennial (n ¼ 1186) low dose CT for a median period of 6 years, or control arm (n ¼ 1723) without intervention.

In the MILD trial, 2005 and 2018, 39 293 person-years of follow-up were accumulated. The primary outcomes were 10-year overall and LC specific mortality. The low dose CT arm showed a 39% reduced risk of LC mortality at 10 years [hazard ratio (HR) 0.61; 95% confidence interval (CI) 0.39–0.95], compared with control arm, and a 20% reduction of overall mortality (HR 0.80; 95% CI 0.62–1.03). The MILD trial provides further evidence that prolonged screening beyond 5 years can enhance the benefit of early detection and achieve a greater overall and LC mortality reduction compared with NLST trial.

**Secondary Care pathways: UK protocols to assist the implementation of LC screening**

The UK national optimal LC pathway (NOLCP) is a timed secondary care pathway approved by NHS England. (Figure 4)

Key features of the early part of the NOLCP include recommendations for rapid access to a CT thorax (within 72h of referral or chest radiograph) and a subsequent triage process. The latter stratifies patients with suspicious CT findings into fast track cancer clinics, with subsequent rapid investigations for and management of LC, or appropriately diverts others from cancer pathways into alternative services. This includes the management of pulmonary nodules according to the British Thoracic Society guideline (23).

**Figure 4**: National Optimal LC Pathway for suspected and confirmed LC: Referral to treatment UPDATE 2017 v2 produced by the Clinical Expert Group for Lung Cancer, NHSE.

The integration of the NOLCP with CT screening provides an opportunity to transform care. As it maximizes the benefits of each and ensures that optimal care is provided to patients throughout their clinical pathway. The current UK cancer waiting times and unwarranted variations in care reflect systemic problems in organisational process and capacity. Thus, this must be driven nationally with regional and local coordination of funding and services.

**Multidisciplinary clinics**: **planning for long-term treatment of CT screened LC patients with a diagnosis of cancer**

It is important that medical oncologists are part of the long-term treatment planning of CT screened patients with a diagnosis of LC; the same is true for radiologists, pulmonologists, surgeons, nuclear medicine physicians and cancer nurses. A critical member of the team is the smoking cessation counsellor as the enhanced feedback associated with annual attention to smoking cessation seems to enhance quit rates. The cost of medical care in older smokers can be significantly reduced (by about one third) by inclusion of best practice smoking cessation advice (24-26) and greatly enhance the cost utility of this integrated screening service.

Large scale implementation of LC screening within nationwide screening programmes in Europe will significantly change the landscape of treatment strategies for patients due to earlier diagnosis. Hopefully, less patients with advanced stages will need more palliative approaches with systemic treatment (chemotherapy, chemo-immunotherapy, immunotherapy) but more patients may need adjuvant and consolidation systemic treatments (stages II, III, chemotherapy, immunotherapy). Furthermore, conversations should also be starting on how to use best practice guidelines to manage the large number of asymptomatic screening subjects who will be found to have objective evidence of chronic obstructive pulmonary disease (COPD) or advanced coronary calcifications. Important trials in the Netherlands (25) and China are already exploring this critical new avenue of public health investigation.

Medical oncologists may also need to shift their interest from the approaches to advanced disease to ‘multidisciplinary approaches’ of stages II, IIIA, IIIB, and IVA of LC. Further clinical trials with systemic treatments for very early LC stages (immunotherapy, chemo-immunotherapy, targeted therapy) can

be foreseen. As new cancer precursors are detected within the screening population, a new generation of chemoprevention trials can be expected. This could potentially include immunological manipulation of the early cancer development process.

**LC biomarkers in early LC detection**

The 'holy grail' in biomarker research is to identify other early detection biomarker(s) beyond the above discussed imaging biomarkers. Despite a massive investment of resources, non-imaging biomarkers have had limited success. A recent systematic review on serum and blood based biomarkers for LC screening provided an excellent update of this topic (27). It evaluated the diagnostic performance of Early CDT-lung (an antibody based biomarker screening panel), micro-ribonucleic acid (RNA) signature classifier (MSC, a plasma-based 24 miRNA risk score), and miR-test (a serum-based 13 miRNA signature), and their impact on LC-related mortality and all-cause mortality. Three phase III studies were identified, and all three biomarker assays show promise for the detection of LC. However, there was a lack of definitive evidence to justify integration into clinical practice.

Seijo and colleagues (28) have recently proposed a number of principles to optimize LC biomarker discovery projects. They provided an overview of promising molecular candidates, such as autoantibodies, complement fragments, microRNAs, circulating tumor deoxyribonucleic acid (DNA), DNA methylation, blood protein profiling, and RNA airway or nasal signatures. The emerging biomarkers, including exhaled breath biomarkers, metabolomics, sputum cell imaging, genetic predisposition studies, and the integration of next-generation sequencing into study of circulating DNA. All of these need to be considered in the scope of future implementation research in LC screening, together with imaging, radiomics, and artificial intelligence (29).

**Recent innovative research programmes: which can impact on future LC screening implementation research**.

***-Early Lung Imaging Confederation (ELIC)***

Since the global implementation of LC screening is only starting just now, there has not been the time nor the resources so far to create specialised imaging tools to enable easy and rapid LC screening management. The Quantitative Imaging Biomarker Alliance (QIBA) organised by the Radiological Society of North America (RSNA) has been working to define scalable solutions to insure robust and accurate use of volumetric CT imaging to guide screening work-up (30), as already published in the UKLS (8) and NELSON trials (3). Large collections of thoracic CT images with known clinical outcomes are urgently needed to develop and validate LC imaging management tools (31).

IASLC is committed to developing a large collection of thoracic CT images to address this bottleneck (32). IASLC with a large multi-disciplinary team has begun to develop the Early Lung Imaging Confederation (ELIC). The goal is to make this cloud-based image collection/ research resource accessible to all IASLC investigators as well as others, as an open resource to accelerate the development of imaging and other tools to manage early LC.

***-Institute of Diagnostic Accuracy Management System (iDNA)***

The iDNA Management System has been developed from the NELSON and UKLS screening trial databases (8, 12). It is a highly configurable client tracking system where clients are screening participants (or patients), and where all types of events are stored in the client's history. This client history contains all relevant details needed for logistical and data management, including features specifically designed for LC screening purposes such as nodule evaluation across multiple evaluations and across multiple scan moments. This allows central review of CT scans, automated calculations on VDTs and automated classification of screening results (based on the optimized NELSON protocol). Secondly, the software is designed to support clear and secure communication between the screening site and the screening participants on undertaking LC risk assessment ($LLP_{v2}$ and $PLCO_{2012}$), making appointments, completion of questionnaires (e.g. on smoking history, and informed consent), reporting on screening results, integration with e-mail and the use of configurable templates for standard notifications and letters. With the iDNA Management System all the screening sites' specific needs on data collection, logistics and communication can be configured by local administrators, ensuring full compliance with local requirements.
Collection of radiological metadata is organised in multiple steps and levels which is based on a direct link between the radiologist's workstation and the iDNA management system: a screening participant can have more than one CT scan record; one CT scan record can have multiple readings/observations and one observation can have multiple nodules and other findings.

The primary application of the iDNA Management system is the registration and management of nodules in LC screening programmes. The iDNA system has been extended with registration and management of calcium scores (for cardiovascular diseases) (33)30) which can be utilised by collaborative screening sites (34). Other radiological features include the validated import of eXtensible Markup Language (XML) files generated by local workstations directly into the study database.

Other comparable systems are being developed including a collaborative effort between the Veterans Administration in the United States working with the International Early LC Action Project with support from the Bristol Myers Squibb Foundation using an open-source software environment.

**GDPR**

The recommendation of a European registry for collection of LC CT screening data was discussed at the roundtable and that the International Association for the Study of Lung Cancer (IASLC) is exploring options in this regard (32). Ideally a registry for screened LC CT images should be developed. However, the changing laws around the EU General Data Protection Regulation (GDPR) are making this more difficult as it is practically impossible to anonymise CT Digital Imaging and Communications in Medicine (DICOM) images. This is a challenge not just within the LC community, it impacts on all radiological imaging and needs to be resolved within the European Parliament. It would be tragic if reasonable measures to ensure personal data protections were to unintentionally delay or even block progress in improving curative outcomes for Europe's most lethal adult cancer.

**Conclusion**

The conclusion reached by the roundtable panel was that national health policy groups in Europe should start to implement CT screening now as adequate evidence is available (4, and figure 1). It was recognised that there are opportunities to improve the 'screening process' through 'Implementation Research Programmes'. Areas which need specific consideration are around cost effectiveness (UKLS data indicates £12,000/ quality-adjusted life year (QALY)) and if biennal screening is appropriate for a subset of individuals with appropriately delivered integrated smoking cessation programmes in place.

**Overall recommendations:**

1. Implementation of LC screening should be a priority in Europe. It this needs to be driven scientifically, politically and also utilising patient advocacy.
2. Europe needs to plan 'Implementation Research Programmes'.
3. Investment is needed into recruitment challenges especially in 'hard to reach' communities.
4. Ensure thoracic radiologists reporting on CT screened individuals utilise volume and VDT and are provided with the necessary training and work with quality assurance procedures are in place.
5. The issues around current GDPR need to be resolved, in order to enable the development of a European registry for collection of LC CT screening data.
6. Secondary Care Pathways are aligned with the imminent implementation of LC screening, together with service provision and availability of screening platforms.
7. Develop a collegiate approach to the work-up and treatment of LC patients in multi-disciplinary clinics, identified through CT screening programmes. All clinical specialties should be fully engaged, including medical oncologists.
8. The role of non-imaging early detection biomarkers is still in an early phase; however, the LC screening community should be fully engaged and participate in the developing integrated research programmes utilising molecular / radiomics and AI approaches.
9. Innovative research programmes (e.g. ELIC and iDNA) provide enormous potential which can impact on LC screening and save lives.
10. LC CT screening will happen in Europe. It is up to the community to make it happen now.

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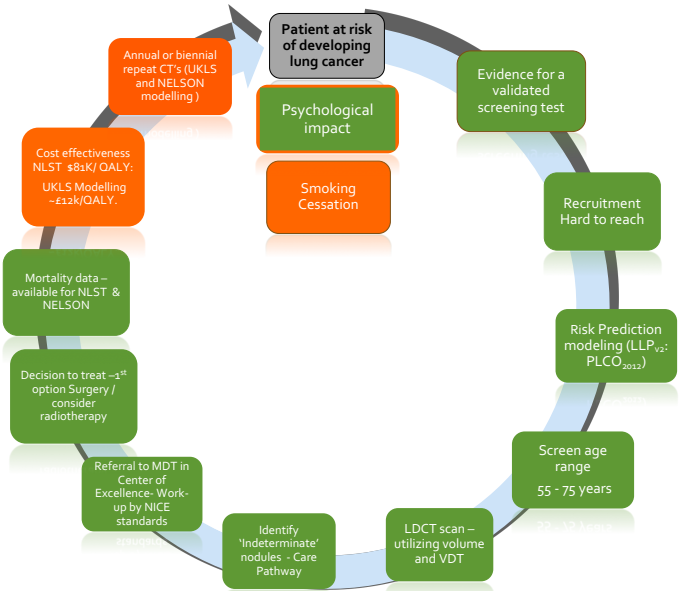
Figure 1




2019 updated : levels of evidence for implementation of lung cancer CT screening in Europe.
Colour codes; green we have sufficient evidence, amber is borderline evidence; red requires further evidence .

Figure 2

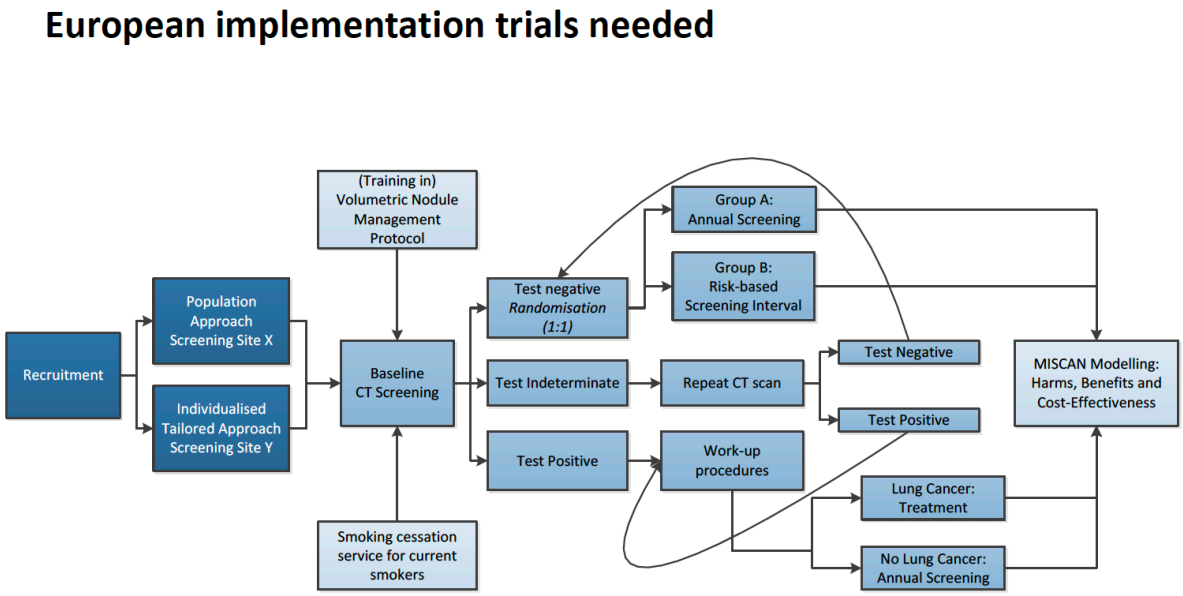

European implementation trials needed
(Training in) Volumetric Nodule Management Protocol
Group A: Annual Screening
Group B: Risk-based Screening Interval
Test negative Randomisation (1:1)
Population Approach Screening Site X
Recruitment
Individualised Tailored Approach Screening Site Y
Baseline CT Screening
Test Indeterminate
Repeat CT scan
Test Negative
Test Positive
MISCAN Modelling: Harms, Benefits and Cost-Effectiveness
Test Positive
Work-up procedures
Lung Cancer: Treatment
No Lung Cancer: Annual Screening
Smoking cessation service for current smokers

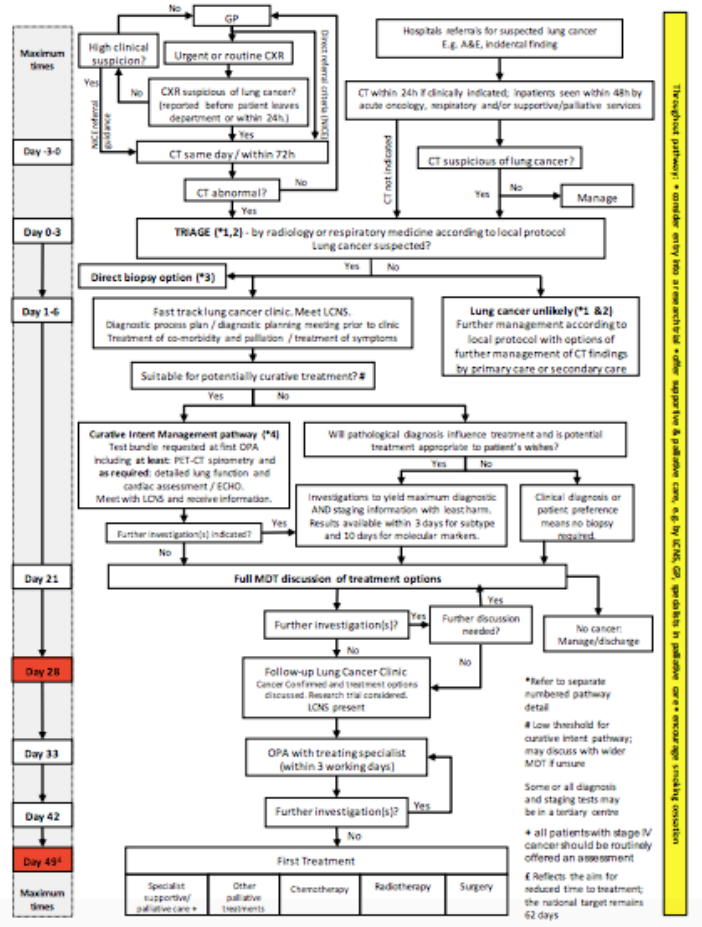
Figure 3

World Congress of Lung Cancer 25th September 2018 Toronto
NLST & NELSON: Lung cancer CT screening Mortality data

| Female v Male ratio | |
|---|---|
| NLST+ | 41/59 |
| | |
| NELSON | 16/84 |

| Percent LC Mortality Decrease | | | |
|---|---|---|---|
| Trial | Men | Women | 50:50 M/F |
| NLST* | 8% | 27% | 18% |
| | | | |
| NELSON** | 26% | 39-61% | 33 – 44% |
| | | | |

Figure 4


Maximum times
Day -3-0
Day 0-3
Day 1-6
Day 21
Day 28
Day 33
Day 42
Day 49£
Maximum times
GP
High clinical suspicion?
Urgent or routine CXR
Direct referral criteria (NICE)
Yes
No
NICE referral guidance
CXR suspicious of lung cancer? (reported before patient leaves department or within 24h.)
Yes
CT same day / within 72h
CT abnormal?
No
Yes
Hospitals referrals for suspected lung cancer E.g. A&E, incidental finding
CT within 24h if clinically indicated; inpatients seen within 48h by acute oncology, respiratory and/or supportive/palliative services
CT not indicated
CT suspicious of lung cancer?
Yes
No
Manage
TRIAGE (*1,2) - by radiology or respiratory medicine according to local protocol
Lung cancer suspected?
Yes
No
Direct biopsy option (*3)
Fast track lung cancer clinic. Meet LCNS.
Diagnostic process plan / diagnostic planning meeting prior to clinic
Treatment of co-morbidity and palliation / treatment of symptoms
Lung cancer unlikely (*1 &2)
Further management according to local protocol with options of further management of CT findings by primary care or secondary care
Suitable for potentially curative treatment? #
Yes
No
Curative Intent Management pathway (*4)
Test bundle requested at first OPA including at least: PET-CT spirometry and as required: detailed lung function and cardiac assessment / ECHO.
Meet with LCNS and receive information.
Will pathological diagnosis influence treatment and is potential treatment appropriate to patient's wishes?
Yes
No
Investigations to yield maximum diagnostic AND staging information with least harm. Results available within 3 days for subtype and 10 days for molecular markers.
Clinical diagnosis or patient preference means no biopsy required.
Further investigation(s) indicated?
Yes
No
Full MDT discussion of treatment options
Yes
Further investigation(s)?
Yes
Further discussion needed?
No cancer: Manage/discharge
No
No
Follow-up Lung Cancer Clinic
Cancer Confirmed and treatment options discussed. Research trial considered.
LCNS present
OPA with treating specialist (within 3 working days)
Further investigation(s)?
Yes
No
First Treatment
Specialist supportive/ palliative care +
Other palliative treatments
Chemotherapy
Radiotherapy
Surgery
*Refer to separate numbered pathway detail
# Low threshold for curative intent pathway; may discuss with wider MDT if unsure
Some or all diagnosis and staging tests may be in a tertiary centre
+ all patients with stage IV cancer should be routinely offered an assessment
£ Reflects the aim for reduced time to treatment; the national target remains 62 days
Throughout pathway: • consider entry into a research trial • refer supportive & palliation care, e.g. by LCNS, GP, geriatric or palliative care • encourage smoking cessation